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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,909	KASIBHATLA ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-13,16-18 and 32-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15 and 19-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/2005 and 8/28/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

1. The election with traverse filed November 20, 2006, is acknowledged and has been entered.

Applicant has elected the invention of Group CCLXXXI, claims 14-15 and 19-31, insofar as they are drawn to a method of identifying potentially therapeutic anticancer compounds comprising contacting the Transferrin Receptor Related Apoptosis Inducing Protein of SEQ ID No: 1 with test compounds, wherein test compounds that bind SEQ ID No: 1 are potentially therapeutic anticancer compounds.

Furthermore, Applicant has elected the species of the invention of Group CCLXXXI, wherein the one or more test compounds is 1-(3-methyl-2-butenyl)-3,3-dimethyl-1,3,3a,4,5,12a-hexahydro-7,13-dioxo-1,5-methano-furo[3,4-d]xanthene.

2. The amendment filed November 20, 2006, is acknowledged and has been entered. Claim 31 has been amended.

3. Claims 1-46 are pending in the application.

4. Claims 1-13, 16-18 and 32-46 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

5. Claims 14-15 and 19-31 are under examination.

Election/Restrictions

6. Upon further consideration of the restriction and election requirement set forth in the Office action mailed September 19, 2006, claims drawn to the invention of Groups CCLXXXII, CCLXXXIII and CCLXXXVIII, drawn to SEQ ID NOS: 2, 3 and 8, which are identical to the sequence of SEQ ID NO:1, have been rejoined with claims drawn to the

elected invention. The restriction and election requirement separating these inventions has been withdrawn.

7. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed September 19, 2006, is acknowledged.

Applicant's arguments have been carefully considered and have been found to be partially persuasive for the following reasons:

The traversal is on the grounds that,

"Applicants respectfully point out to the Examiner that SEQ ID NOS:1-26 are related sequences" and that "As seen from the alignments, SEQ ID NOS:1, 2, 3 and 8 are identical sequences". Finally, applicants argue that "Therefore, a search of SEQ ID NO: 1 would necessarily be coextensive with a search for these sequences as well".

Since, the alignments confirm that SEQ ID NOS: 2, 3 and 8 are identical to SEQ ID NO:1 the argument for rejoining these sequences is persuasive. However, as confirmed by the sequence alignments the other sequences are not identical to SEQ ID NO:1 and therefore would require separate sequence searches that contrary to applicant's assertions are not coextensive with a search of SEQ ID NO:1. Furthermore, these sequences would also require the consideration of different issues to determine their patentability. Therefore, a search of more than one sequence presents an undue burden on the Patent and Trademark Office due to the complex nature of the search in terms of computer time needed to perform the search and the subsequent analysis of the search results by the Examiner. For these reasons, the argument to rejoin all of SEQ ID NOs:1-26 with the elected invention was not found persuasive.

Clearly different searches and issues are raised in the examination of each group, which would create a burden on the Office. See MPEP 808.02.

Beyond the rejoinder of SEQ ID NOS: 2, 3 and 8, the restriction and election requirement set forth in the Office action mailed September 19, 2006, is deemed proper and therefore made **FINAL.**

Information Disclosure Statement

8. The references cited in the information disclosure statements filed on July 21, 2005 and August 28, 2006, have been considered.

Priority

9. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit back to the earlier filing date of U.S. Provisional Application No. 60/463,649, filed April 18, 2003, is acknowledged.

However, claims 14-15 and 19-31 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, claim 31 does not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since compounds to which the claim is directed are not disclosed in U.S. Provisional Application No. 60/532,665, filed December 29, 2003.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely April 19, 2004.

Specification

10. The disclosure is objected to because of the following informalities:

(a) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such an improperly demarcated trademarks appearing in the specification include Gleevec™ and Iressa™ (see, e.g., page 54).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

(b) The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appear in the specification at, for example, paragraph [0331] and paragraph [0572] of the published application, U.S. Patent Application Publication No. 2005/0004026, which is viewable at http://appft1.uspto.gov/netahtml/PTO/search-bool.html.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

(c) The abstract of the disclosure is objected to because it exceeds 150 words in length. See MPEP § 608.01(b).

(d) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

11. Claims 14-15 and 19-31 are objected to as encompassing the subject matter of non-elected inventions.

12. Claims 20 and 22 are objected to because of the omission of an article (e.g., *the*) prior to the term "TRRAIP". Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 26-29 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 26-29 are indefinite because claims 26 and 28 are directed to an assay according to claim 20 and 22, respectively, which "comprises gambogic acid having a detectable label or a gambogic acid-related compound having a detectable label". This recitation renders the claims indefinite because it is cannot be ascertained how the "assay" is necessarily characterized as comprising one or the other of these compounds; moreover, the claims fail to set forth an active process step requiring the use of one or the other of these compounds. How is gambogic acid having a detectable

label or a gambogic acid-related compound having a detectable label used in the claimed process? The claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

(b) Claim 19 is indefinite because of the use of the term "transferrin receptor protein". The use of the term to identify the protein to which the claim is directed renders the claim indefinite because it fails to point out with the requisite particularity the identity of the protein. Different laboratories often use the same nomenclature to identify distinct proteins. In this instance, the term "transferrin receptor" is used in the relevant art to identify at least two different proteins, TfR1 and Tfr2. Johnson et al. (*Mol. Biol. Cell.* 2006 Dec 20; electronically published ahead of print; see PUBMED ID. NO. 17182845) teaches TfR1 and TfR2 are structurally and functionally distinct proteins, since, for example, although TfR2 also binds diferric transferrin, it appears to function primarily in the regulation of systemic iron homeostasis; see entire document (e.g., the abstract). Accordingly, because it is unclear or cannot be ascertained to which of the different proteins termed "transferrin receptor protein" the claim is directed, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

It is suggested that this issue be remedied by amending claim 19 to recite a limitation requiring the "transferrin receptor protein" to comprise a particular amino acid sequence, which is disclosed in the specification, as filed, because such a limitation would serve to unambiguously identify the protein to which the claim is directed.

(c) Claim 31 is indefinite because it recites the limitation "said compound". There is insufficient antecedent basis for this limitation in the preceding claim because claim 14 recites two distinct types of "compounds", (i.e., "potentially therapeutic anticancer compounds" and "test compounds") and it is unclear if the limitation, "said compound", is directed to the "potentially therapeutic anticancer compounds" or the "test compounds". As such, it is submitted that the claims fail to delineate the metes and

bounds of the subject matter that Applicant regards as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 14, 15, and 19-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the

applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In the instant case, claims 14 and 20-31 are drawn to processes comprising contacting any of a broad genus of "Apoptosis Inducing Proteins (AIPs)" with one or more test compounds and monitoring whether said one or more test compounds bind to said AIP to identify compounds that bind to said AIP as potentially therapeutic anticancer compounds, whereas claim 15 is drawn to processes comprising contacting

the members of the broad genus of AIPs, which are "Transferrin Receptor Related Apoptosis Inducing Proteins (TRRAIPs)" with one or more test compounds.

In contrast to the breadth of the claims, the specification only adequately describes with the requisite particularity one member of the genus of "AIPs", which is a member of the subgenus of "TRRAIPs", namely the transferrin receptor protein.

The specification on page 14 describes members of the genus of "AIPs" as inclusive of various different pluralities of other proteins, including "Transferrin Receptor Related Apoptosis Inducing Proteins (TRRAIPs)", "Clathrin Heavy Chain Related Apoptosis Inducing Proteins (CHCRAIPs)", "IQ motif containing GTPase Activating Protein Related Apoptosis Inducing Proteins (IQGAPRAIPs)", and "Heat Shock Protein Related Apoptosis Inducing Proteins (HSPRAIPs)".

Notably, members of the subgenus of "TRRAIPs" are not described as having any structural or functional similarity with members of any of other pluraltities of "AIPs", such as members of the subgenus of HSPRAIPs.

Given the lack of particularity with which the genus of "AIPs" is described, it is submitted that the claim 14 is directed to any protein that might be capable of inducing apoptosis directly or indirectly, or any protein associated with the induction of apoptosis. "Apoptosis Inducing Proteins" makes the genus inclusive of any proteins linked to inducing apoptosis. Hinoda et al (Cancer Science, 95(8):621-625, 2004), for example, describes HER2 as such a protein, teaching that contacting HER2 with anti-HER2 monoclonal antibodies induced apoptosis (see entire document, e.g., abstract, page 622). Therefore, HER2 is an reasonably considered a member of the genus of "AIPs" to which claim 14 is directed. Notably HER2 shares no substantial structural similarity with Transferin Receptor (TfR), the only particularly described "AIP", which is a member of the subgenus of "TRRAIPs". Furthermore, despite the fact that both are receptors, and are known to be associated with the induction of apoptosis, HER2 and TfR not fairly considered to have functional equivalency or even substantially related activities.

Accordingly, the genus of AIPs includes members, having substantially and significantly variant structures and/or functions. The specification fails to adequately describe this genus, as a whole, because the skilled artisan could not immediately

envision, recognize or distinguish as least most of its members from other proteins, as the specification fails to describe its members as sharing any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of those proteins.

As noted above, apart from claim 14, the rejected claims are directed to the subgenus of "TRRAIPs", which are "Transferrin Receptor Related Apoptosis Inducing Proteins (TRRAIP)". In contrast to claim 19, which is specifically directed to "transferrin receptor protein", claims 15 and 20-31 are directed to a genus of structurally and/or functionally disparate proteins, which include proteins that either unknown or not well described and otherwise characterized.

At paragraph [0055] of the published application, for example, the specification describes the genus of "TRRAIPs" as inclusive of polypeptides comprising the amino acid sequences of SEQ ID NO: 1 or 4 and mutants, homologs, derivatives or fragments thereof, which affect apoptosis upon binding gambogic acid (GA) or GA-related compounds such as those described herein or in U.S. Patent No. 6,462,041.

Then, at paragraph [0273] of the published application, the specification further describes the mutants of the polypeptides of SEQ ID NO: 1 or SEQ ID NO: 4 as inclusive of polypeptides that differ from the polypeptides of SEQ ID NO: 1 or SEQ ID NO: 4 by one or more amino acid substitutions, which are naturally occurring (e.g., allelic variants) or artificially generated. At paragraph [0274] of the published application, the specification further describes the homologs of the polypeptides of SEQ ID NO: 1 or SEQ ID NO: 4 as inclusive of any polypeptide having an amino acid sequence that is at least 70% homologous to the amino acid sequence of SEQ ID NO: 1 or 4. At paragraph [0280] of the published application, the specification further describes the derivatives of the polypeptides of SEQ ID NO: 1 or SEQ ID NO: 4 as inclusive of any derivatized or modified forms of the polypeptides of SEQ ID NO: 1 or 4, which are produced, for example, following post-expression modifications, such as the addition of amidated carboxyl groups, glycosylated amino acid residues, and formylated and acetylated amino groups. The fragments of the polypeptides of SEQ ID NO: 1 or SEQ ID NO: 4 are described as any oligopeptide or polypeptide comprising an amino

acid sequence comprising fewer amino acids than the number of amino acids in the full length sequences of SEQ ID NO: 1 or SEQ ID NO: 4, but which are not necessarily identical to an amino acid sequence of a fragment of either sequence; see paragraph [0281] of the published application.

Thus, claims 15 and 20-31 are directed to a genus of structurally and functionally varying proteins.

Because of the substantial differences in the structures of members of the genus of "TRRAIPs", "transferrin receptor protein" is not reasonably considered representative of the genus, as a whole, since, for example, the specification fails to describe any one particularly identifying structural feature of "transferrin receptor protein", which is shared by other members of the genus, and which correlates with any one common particularly identifying functional feature (e.g., the ability to deliver iron to cells through receptor-mediated endocytosis of diferric transferrin, as is the function of TfR-1).

For these reasons, the skilled artisan could not immediately envision, recognize or distinguish the members of the genus of "TRRAIPs" to which claims 15 and 20-31 are directed, and consequently the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Additionally, the rejected claims are directed to a process for identifying potentially therapeutic anticancer compounds. The process comprises contacting an "AIP" such as "transferrin receptor protein" with a test compound and monitoring binding of the test compound to the protein. Notably the test compound to which any of claims are directed need not actually be capable of binding to the protein, as the claims only require that the ability or inability of the protein to do so be monitored. Nevertheless, as discussed in greater detail below, the mere ability of a test compound to bind to an "AIP" (e.g., "transferrin receptor protein") does not alone provide an indication that the compound is capable of inducing the apoptosis of cells expressing the protein, and would not necessarily provide an indication that the test compound might be therapeutically useful in treating cancer. As such, it is submitted that it should not be

considered sufficient to merely describe the test compounds to which the claims are directed as *perhaps* capable of binding the protein.

The inventive concept is based upon Applicant's discovery that gambogic acid, derivatives thereof, and/or other structurally related compounds, which are capable of inducing the onset of apoptosis in cells, bind to "transferrin receptor", which is expressed at the surface of the susceptible cells. None of the claims, apart from claim 19, require the use of "transferrin receptor" however; and moreover, none of the claims, apart from claim 31, clearly require the use of test compounds that are allegedly related in structure to gambogic acid. So, while claim 14, for example, is broadly drawn to a process for assessing the ability of any test compound to bind to any "AIP", so as to be identified as having potential anticancer therapeutic value, the specification has not particularly described test compounds that bind proteins other than "transferrin receptor", nor has it particularly described test compounds other than compound related in structure to gambogic acid, which bind to "transferrin receptor". For these reasons, the specification would amount to no more than a mere invitation to the skilled artisan to discover the identity of other proteins that might be used to screen test compounds that are therapeutically useful, or to discover the identity of other types of test compounds, which are not structurally related to gambogic acid, but nonetheless bind to "transferrin receptor" to induce the onset of apoptosis in cells expressing that protein.

Furthermore, while the specification indicates that the subgenus of TRRAIPs includes mutants, homologs, derivatives and fragments of "transferrin receptor protein", it does not describe with any particularity the structural modifications that can be made to the transferrin receptor to obtain mutants, homologs, derivatives or fragments that would still function to affect apoptosis upon binding gambogic acid (GA) or GA-related compounds.

Notably, the description of such compounds as having an ability to *affect* apoptosis implies that the compounds may have the ability to promote or inhibit apoptosis, yet the specification only reasonably conveys that possession of potentially therapeutic anticancer compounds, which include gambogic acid (GA) or GA-related compounds, that bind to "transferrin receptor" to promote apoptosis; and there are no

test compounds, such as gambogic acid (GA) or GA-related compounds, which have been particularly described as capable of inhibiting apoptosis.

For these reasons, the specification would only reasonably convey possession of a process by which potentially therapeutic compounds, which are structurally related to gambogic acid and capable of binding "transferrin receptor protein" to induce apoptosis in the cells expressing the protein, are identified (see Table 1 pages 165 and 166 and Table II pages 167 and 168).

Further, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of affecting apoptosis upon binding gambogic acid (GA) or GA-related compounds does not distinguish transferrin receptor protein mutants, homologs, derivatives and fragments from others having the same activity or function and as such, fails to satisfy the written description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed subgenus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Structural features that could distinguish transferrin receptor protein mutants, homologs, derivatives and fragments that affect apoptosis upon binding gambogic acid (GA) or GA-related compounds are missing from the disclosure and the claims. No common structural attributes identify the members of the subgenus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure does not

describe the common attributes or structural characteristics that identify members of the genus, and because the genus and subgenus are highly variant, the function of affecting apoptosis upon binding gambogic acid (GA) or GA-related compounds is insufficient to describe the subgenus. One of skill in the art would reasonable conclude that the disclosure of the transferrin receptor protein that upon binding gambogic acid (GA) or GA-related compounds increases apoptosis, does not provide a representative number of species of all transferrin receptor protein mutants, homologs, derivatives and fragments that would be sufficient to describe the claimed subgenus.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). In this instance, while the specification describes the structure the transferrin receptor protein, one cannot predict what structure is common to all transferrin receptor protein mutants, homologs, derivatives and fragments that could be used in the claimed method.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, while the specification describes the transferrin receptor protein as being able to identify potentially therapeutic anticancer compounds, the skilled artisan cannot predict which transferrin receptor protein mutants, homologs, derivatives and fragments would retain this ability to identify potentially therapeutic anticancer compounds.

Given the lack of particularity with which the AIPs and TRRAIPs, to which the claims are directed, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of AIPs or the subgenus of TRRAIPs to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

17. Claims 14-15 and 19-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for identifying potentially therapeutic anticancer compounds, said method comprising contacting "transferrin receptor protein" (i.e., the polypeptide of any of SEQ ID NOs: 1, 2, 3 or 8) with gambogic acid (GA) or structurally-related test compounds that have or retain the ability to bind the protein and determining whether said contact induces a cancer cell expressing the protein to undergo apoptosis, whereby if the cancer cell undergoes apoptosis the compound is identified as a potentially therapeutic anticancer compound, **and while being enabling for using** any such process and assay system

encompassed by the claims, which has been described by the prior art, **does not reasonably provide enablement for using** the claimed processes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

For the reasons set forth in the above rejection of the claims, as failing to satisfy the written description requirement, it has been submitted that the specification would amount to no more than a mere invitation to the skilled artisan to discover the identity of

other "Apoptosis Inducing Proteins" that might be used to screen test compounds that are therapeutically useful, or to discover the identity of other types of test compounds, which are not structurally related to gambogic acid, but nonetheless bind to "Apoptosis Inducing Proteins", such as "transferrin receptor protein" to induce the onset of apoptosis in cells expressing that protein.

Applicant is reminded reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

While the specification indicates that the subgenus of TRRAIPs includes mutants, homologs, derivatives and fragments of "transferrin receptor protein", it does not particularity describe the structural modifications that can be made to the "transferrin receptor protein" (e.g., the polypeptide of SEQ ID NO: 1) without loss of function (i.e., the ability to bind gambogic acid (GA) or GA-related compounds and/or to induce apoptosis after binding such compounds). The artisan cannot predict whether any given protein is associated with apoptosis; and many proteins have no apparent direct or indirect role in the process by which cells undergo programmed cell death. Furthermore, even in instances where a given protein is known to function in process, the artisan cannot predict whether the protein may be used to screen "test compounds" to identify those that are potentially therapeutic. Consequently, the amount of guidance, direction, and exemplification is not sufficient to reasonably enable the skilled artisan to make and then use any protein, other than "transferrin receptor protein" to screen test compounds to identify those having potential anticancer therapeutic value.

Furthermore, whereas the claims are directed to any test compound, and not necessarily a test compound that is capable of binding the "AIP" (e.g., "transferrin receptor protein), the specification only describes gambogic acid (GA) or GA-related compounds capable of binding "transferrin receptor protein", so the amount of guidance, direction and exemplification set forth in the specification is not reasonably commensurate in scope with the breadth of the claims. Unless a compound is structurally related to gambogic acid or other known ligands of the receptor (e.g., diferric transferrin; anti-Tfr1 antibodies), it is submitted that the skilled artisan could not reasonably predict whether the compound will be capable of binding "transferrin receptor protein". The specification teaches a biotinylated derivative of gambogic acid, which does not bind "transferrin receptor protein" and is incapable of inducing the apoptosis of cells expressing the receptor. And, if it cannot be predicted whether the compound binds the protein, it cannot be predicted whether the screening process that is the claimed invention can be used to identify compounds having potential therapeutic value because compounds that do not bind the protein are not reasonably expected to affect apoptosis in a cancer cell by a mechanism that is dependent upon the activity of the protein. For example, as noted below, an antibody that binds Tfr1 does not induce cells expressing the receptor to undergo apoptosis.

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify other assay systems encompassed by the claims comprising "Apoptosis Inducing Proteins" that bind to test compounds exemplified by known compounds that have been recognized as having the ability to induce apoptosis of cells expressing those protein upon contact by the compounds.

The specification teaches no exemplary test compounds, such as gambogic acid (GA) or GA-related compounds, which are described as capable of inhibiting apoptosis. As such, the amount of guidance, direction, and exemplification would, at best, be sufficient only to permit the skilled artisan to make and test compounds having potentially therapeutic anticancer activity, which bind to "transferrin receptor" to *promote* apoptosis.

Instead, the specification only teaches a number of compounds, such as those specifically recited in claim 31, which allegedly retain the ability of gambogic acid to bind to "transferrin receptor protein" or some other "TRRAIP" to induce the apoptosis of cells expressing the receptor. It does not appear, however, that the specification provides a disclosure of factual evidence supporting the assertion that any of the particularly described "derivatives" of gambogic acid retain its ability to bind "transferrin receptor protein" to induce the apoptosis of cells expressing the protein. As noted above, the specification teaches a biotinylated derivative of gambogic acid, which does not have or retain the activity of the parent compound, suggesting the skilled artisan cannot predict the consequence of structural modifications of gambogic acid but would have need to empirically determine whether any compound structurally related to gambogic acid binds to "transferrin receptor protein" and/or is capable of inducing "transferrin receptor protein"-mediated apoptosis in cells expressing the protein.

For these reasons, the specification would only reasonably enable the skilled artisan to identify potentially therapeutic compounds, which are structurally related to gambogic acid and capable of binding "transferrin receptor protein" to induce apoptosis in the cells expressing the protein.

Therefore, to the extent that the claims are drawn to a method comprising contacting "transferrin receptor protein" with test compounds and monitoring whether said compounds bind to the transferrin receptor protein, it is important to note that whereas the specification discloses that test compounds comprise any natural product, synthesized organic or inorganic molecule, or biological macromolecules (see page 16, second paragraph), the specification only shows that contacting "transferrin receptor protein" with gambogic acid (GA) or GA-related compounds that bind to protein causes apoptosis in cells (see Table 1 pages 165 and 166 and Table II pages 167 and 168).

Ng et al (PNAS, 99(16):10706-10711, 2002) teach that a transferrin receptor antibody that binds transferrin receptor, which would be considered a biological macromolecule, does not induce apoptosis in cells expressing transferrin receptor, unless the transferrin receptor antibody is conjugated to avidin (see entire document, e.g., abstract and page 10708, second column, bridging paragraph). Furthermore, the

protein transferrin, a known the ligand for the transferrin receptor, is not cytotoxic to cells.

In view of the fact that not all compounds that bind transferrin receptor are potentially therapeutic anticancer compounds, it is apparent that the skilled artisan cannot predict whether or not a compound that binds the transferrin receptor has any potential for use as a therapeutic anticancer compound unless that compound is structurally related to gambogic acid and retains the ability to bind transferrin receptor. As such, unless the process necessarily involves an active step by which it is determined whether the test compound induces apoptosis of cancer cells expressing the protein, the process cannot be used in a predictable manner to identify those test compounds that have potential therapeutic anticancer value.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 14-15, 19-23 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Faulk (US Patent 5,000,935, published March 19, 1991) as evidenced by Merino et al (WO2004009622-A2, published 2004).

Here, the claims are drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with one or more bioconjugate test compounds and monitoring whether said compounds bind to the transferrin receptor protein in a homogenous radioassay or a competitive heterogeneous radioassay, to identify potentially therapeutic anticancer compounds. Claim 30 is herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with one or more bioconjugate test compounds and monitoring whether said compounds bind to the transferrin receptor protein wherein the transferrin receptor protein is present in cells *in vitro*, to identify potentially therapeutic anticancer compounds.

Support for this interpretation occurs in the specification where it characterizes test compounds as comprising any natural product, synthesized organic or inorganic molecule, or biological macromolecule and that bioconjugates are potential anticancer agents (see page 16, second paragraph and page 56-57, bridging paragraph). Furthermore, the specification characterizes homogeneous assays as assays with the components mixed together in the same phase (e.g., the aqueous layer of a biphasic system comprising aqueous and organic phases) and heterogeneous assays as comprising assays in which one component is attached to a solid substrate, such as a bead, and one or more additional components are in solution (see page 44, first paragraph).

Faulk teaches contacting a transferrin receptor protein that is expressed on the surface of cells *in vitro* with an ^{125}I-transferrin bioconjugate and monitoring whether the ^{125}I-transferrin conjugate binds to the transferrin receptor protein, which identifies the ^{125}I-transferrin bioconjugate as a potentially therapeutic anticancer compound because the radiolabel is cytotoxic to the cells targeted (see entire document, e.g., column 1, 2, 5 and 7). Faulk also teaches contacting purified transferrin receptor with the ^{125}I-transferrin conjugate *in vitro* and monitoring the binding, an assay which is considered a homogeneous radioassay because the purified transferrin receptor and the ^{125}I-transferrin bioconjugate are in solution (i.e., the same phase) (e.g., column 2). Finally Faulk teaches contacting cells expressing a transferrin receptor protein in a xenograft

mouse model with the ^{125}I-transferrin conjugate and monitoring whether the ^{125}I-transferrin bioconjugate binds to the cells, an assay system considered a competitive heterogeneous assay system because *in vivo* the ^{125}I-transferrin conjugate competes with naturally occurring transferrin for binding to the transferrin receptor, which is attached to a solid substrate (i.e., the animal's cells), and the ^{125}I-transferrin bioconjugate and transferrin are in solution (i.e., the animal's plasma). Finally, as evidenced by Merino et al the transferrin receptor sequence is 100% identical to SEQ ID NOS: 1, 2, 3 and 8 of the instant application (see Exhibit A).

Therefore, Faulk anticipates these claims.

20. Claims 14-15, 19, 22-23 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Vaughan et al (In. J Radiation Oncology Biol. Phys. 8:1943-1946, 1982) as evidenced by Merino et al (WO2004009622-A2, published 2004).

Here, the claims are drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with one or more bioconjugate test compounds and monitoring whether said compounds bind to the transferrin receptor protein in a competitive heterogeneous radioassay, to identify potentially therapeutic anticancer compounds. Claim 30 is herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with test compounds and monitoring whether said compounds bind to the transferrin receptor protein wherein the transferrin receptor protein is present in cells *in vitro*, to identify potentially therapeutic anticancer compounds.

Vaughan et al teach contacting a transferrin receptor protein that is expressed on the surface of cells *in vitro* with a ^{211}At-transferrin receptor antibody bioconjugate and monitoring whether ^{211}At-transferrin receptor antibody binds to the transferrin receptor protein in a competitive heterogeneous radioassay comprising unlabeled antibody. The assay of Vaughan is heterogeneous because the cells were incubated as a pellet with the ^{211}At-transferrin receptor antibody bioconjugate and therefore where not in solution. Vaughan et al also teach that the ^{211}At-transferrin receptor antibody causes cell death in the cells targeted, which identifies the ^{211}At-transferrin receptor antibody bioconjugate.

as a potentially therapeutic anticancer compound (see entire document, e.g., abstract, page 1944, first column and figure 2). Finally, as evidenced by Merino et al the transferrin receptor sequence is 100% identical to SEQ ID NOS: 1, 2, 3 and 8 of the instant application (see Exhibit A).

Therefore, Vaughan et al anticipate these claims.

21. Claims 14-15 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Ng et al (PNAS, 99(16):10706-10711, 2002) as evidenced by Merino et al (WO2004009622-A2, published 2004).

The claims are herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with one or more bioconjugate test compounds and monitoring whether said compounds bind to the transferrin receptor protein, to identify potentially therapeutic anticancer compounds. Claim 30 is herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with one or more bioconjugate test compounds and monitoring whether said compounds bind to the transferrin receptor protein wherein the transferrin receptor protein is present in cells *in vitro*, to identify potentially therapeutic anticancer compounds.

Ng et al teach contacting a transferrin receptor protein that is expressed on the surface of cells *in vitro* with a transferrin receptor antibody-avidin fusion protein and monitoring whether the transferrin receptor antibody-avidin fusion protein binds to the transferrin receptor protein. Ng et al also teach that the transferrin receptor antibody without avidin fused does not induce apoptosis in cells that express transferrin receptor, while the transferrin receptor antibody-avidin fusion protein does, which identifies the transferrin receptor antibody-avidin fusion protein as a potentially therapeutic anticancer compound. Finally, as evidenced by Merino et al the transferrin receptor sequence is 100% identical to SEQ ID NOS: 1, 2, 3 and 8 of the instant application (see Exhibit A).

Therefore, Ng et al anticipate these claims.

22. Claims 14-15, 19-20 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Cai et al (US Patent 6,462,041, issued October 8, 2002, IDS filed 7/21/2005) as evidenced by Kasibhatla et al (a) (PNAS, 102(34):12095-12100, 2005 IDS filed 8/28/2006) and Merino et al (WO2004009622-A2, published 2004).

The claims are herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with test compounds and monitoring whether said compounds bind to the transferrin receptor protein in a homogenous assay, to identify potentially therapeutic anticancer compounds. Claim 30 is herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with test compounds and monitoring whether said compounds bind to the transferrin receptor protein wherein the transferrin receptor protein is present in cells *in vitro*, to identify potentially therapeutic anticancer compounds

Cai et al teach contacting the tumor cell line, T47D, *in vitro* with gambogic acid and monitoring cell proliferation and caspase activity in the T47D cell line to identify gambogic acid as a potentially therapeutic anticancer compound (see entire document, e.g., column 77, 81 and tables II and IV). The assays of Cai are considered homogenous because the T47D cells were suspended in solution and then added to wells containing gambogic acid in solution, so at the beginning of the assay all components were in the same phase. As evidenced by Kasibhatla et al (a), the T47D cell line expresses the transferrin receptor (see entire document, e.g., page 12098, right column) and as evidenced by Merino et al the transferrin receptor sequence is 100% identical to SEQ ID NOS: 1, 2, 3 and 8 of the instant application (see Exhibit A). While Cai et al is silent about whether gambogic acid binds the transferrin receptor, the ability of gambogic acid to bind the transferrin receptor and cause apoptosis is an inherent property of gambogic acid as evidenced by Kasibhatla et al (a) (e.g., page 12095, first column), so by monitoring the outcome of contacting the cells with gambogic acid Cai is indirectly monitoring whether the compound binds the transferrin receptor and identifying it as a potentially therapeutic anticancer compound.

Therefore, Cai et al anticipate these claims.

23. Claims 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Cai et al (US Patent 6,462,041, issued October 8, 2002, IDS filed 7/21/2005) as evidenced by Hinoda et al (Cancer Science, 95(8):621-625, 2004) . .

Claim 14 is herein drawn to a method comprising contacting an Apoptosis Inducing Protein with one or more bioconjugate test compounds and monitoring whether said compounds bind to said AIP, to identify potentially therapeutic anticancer compounds.

Cai et al teach contacting cells with bioconjugate test compounds comprising the antibody trastuzumab and gambogic acid-related compounds and monitoring their binding to the cell surface to identify potentially therapeutic anticancer compounds (see entire document, column 21). As evidenced by Hinoda et al, trastuzumab binds to HER2 on the cell surface of cells and induces apoptosis, making HER2 an Apoptosis Inducing Protein (see entire document, e.g., abstract and page 622), so Cai is contacting HER2 with a bioconjugate test compound and monitoring the compounds ability to bind HER2.

Therefore, Cai et al anticipate this claim.

24. Claims 14-15, 19 and 30 are rejected under 35 U.S.C. 102(a) as being anticipated by Kasibhatla et al (b) (Clinical Cancer Research, 9:6164S #B107, December 1, 2003) as evidenced by Xu et al (Molecular Cancer Therapeutics, 1:337-346, March 2002) and Merino et al (WO2004009622-A2, published 2004).

The claims are herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with test compounds and monitoring whether said compounds bind to the transferrin receptor protein, to identify potentially therapeutic anticancer compounds. Claim 30 is herein drawn to a method comprising contacting the transferrin receptor protein of SEQ ID NOS: 1, 2, 3 and 8 with test compounds and monitoring whether said compounds bind to the transferrin receptor protein wherein the transferrin receptor protein is present in cells *in vitro*, to identify potentially therapeutic anticancer compounds.

Kasibhatla et al (b) teach contacting a prostate cancer cell line with MX-2167, a gambogic acid-related compound and monitoring cell proliferation in this cell line to identify MX-2167 as a potentially therapeutic anticancer compound (see abstract). As evidenced by Xu et al, prostate cancer cell lines express the transferrin receptor (see entire document, e.g., page 344, left column and figure 6) and as evidenced by Merino et al the transferrin receptor sequence is 100% identical to SEQ ID NOS: 1, 2, 3 and 8 of the instant application (see Exhibit A). While Kasibhatla et al (b) is silent about whether MX-2167 binds the transferrin receptor, the ability of gambogic acid-related compounds to bind transferrin receptor and cause apoptosis is an inherent property of the compounds, so by monitoring the outcome of contacting the cells with MX-2167, Kasibhatla et al (b) is indirectly monitoring whether MX-2167 binds the transferrin receptor and identifying MX-2167 as a potentially therapeutic anticancer compound.

Therefore, Kasibhatla et al (b) anticipate these claims.

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

26. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 14-15 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faulk (US Patent 5,000,935, published March 19, 1991), in view of Shyjan (US Patent 6,458,939, published October 1, 2002).

The claims are herein drawn to a method comprising contacting a TRRAIP with test compounds and monitoring whether said compounds bind to said TRRAIP, wherein said TRRAIP comprises a fluorescent label or a radiolabel, to identify potentially therapeutic anticancer compounds.

Faulk teaches what is set forth in the 102(b) rejection supra. Faulk does not expressly teach labeling the transferrin receptor protein, a species of TRRAIP with a fluorescent label or a radiolabel. This deficiency is made up for in the teachings of Shyjan.

Shyjan teaches that proteins can be labeled with radiolabels or fluorescent labels to facilitate detection of complexes formed between the protein and test substances. (see entire document, e.g., column 20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to label the transferrin receptor protein with radiolabels or fluorescent labels in order to facilitate detection of complexes formed between the transferrin receptor protein and test compounds.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to label the transferrin receptor protein with the radiolabels or the fluorescent labels of Shyjan because Shyjan

teaches that this facilitates detection of complexes formed between the protein and test substances (e.g., column 20) and methods to successfully label proteins were common at the time the invention was made.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

28. Claims 14-15, 22-23 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cai et al (US Patent 6,462,041, issued October 8, 2002, IDS filed 7/21/2005), in view of Kasibhatla et al (b) (Clinical Cancer Research, 9:6164S #B107, December 1, 2003) and Shyjan (US Patent 6,458,939, published October 1, 2002).

Claims 14-15 and 22-23 and 26-29 are herein drawn to a method comprising contacting a TRRAIP with test compounds and monitoring whether said compounds bind to said TRRAIP in competitive heterogeneous fluorescence polarization assays or radioassays comprising a gambogic acid-related compound having a fluorescent label or radiolabel, to identify potentially therapeutic anticancer compounds.

Cai et al teach what is set forth in the 102(b) rejection of claims 14-15 supra. Cai et al do not expressly teach competitive heterogeneous fluorescence polarization assays or radioassays comprising a gambogic acid-related compound having a fluorescent label or radiolabel. These deficiencies are made up for in the teachings of Kasibhatla et al (b) and Shyjan.

Kasibhatla et al (b) teach contacting cells expressing a TRRAIP with MX-2167, a gambogic acid-related compound and assays comprising, MX-2167.

Shyjan teach that compounds can be labeled with radiolabels or fluorescent labels and used in competitive heterogeneous fluorescence polarization assays or radioassays to determine if a compound competes with another (see entire document, e.g., column 20, 25 and 26).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to label the gambogic acid-related compound, MX-2167 of Kasibhatla and use it a competitive heterogeneous fluorescence

polarization assay or radioassay of Shyjan to determine if MX-2167 could compete with gambogic acid.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention made to label MX-2167 with radiolabels or fluorescent labels and use it in a competitive heterogeneous fluorescence polarization assay or radioassay to determine if MX-2167 could compete with gambogic acid because Shyjan teaches that this can identify compounds that interfere with a known interaction (e.g., column 26).

Furthermore, there would also be a reasonable expectation of success because it was common to label compounds at the time the invention was made and since Cai teaches that many gambogic acid-related compounds have similar functional properties to gambogic acid one would be motivated to test MX-2167 for its ability to compete with gambogic acid and would have a reasonable expectation that it would compete with gambogic acid.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

29. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

30. Claim 14 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-20 of copending Application No. 11/525,140. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 10-20 of copending Application No. 11/525,140 are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claim is described supra.

Claims 10-20 of copending Application No. 11/525,140 are drawn to methods comprising contacting a Tail Interacting Protein Related Apoptosis Inducing Protein (TIPRAIP) with one or more test compounds and monitoring whether said one or more compounds binds to said TIPRAIP, wherein compounds which bind said TIPRAIP are potential therapeutic anticancer compounds.

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed

subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

Conclusion

31. No claims are allowed.

32. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Trowbridge et al (US Patent 4,434,156, 1984, IDS filed 7/21/2005) teach antibodies to the transferrin receptor. Trowbridge et al (US Patent 5,648,469, 1997, IDS filed 7/21/2005) teach antibodies to the transferrin receptor. Trowbridge et al (US Patent 5,667,781, 1997, IDS filed 7/21/2005) teach inhibition of tumor cell proliferation using a combination of two monoclonal antibodies to the human transferrin receptor.

The art made of record and not relied upon is considered pertinent to applicant's disclosure. Cai et al (Current Medicinal Chemistry, 13:2627-2644, 2006) disclose the gambogic acid-related compound MX2167 (also referred to as EP2167).

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

STEPHEN L. RAWLINGS, PH.D.
PRIMARY EXAMINER

Exhibit A

<!--StartFragment-->RESULT 3
ADJ66570
ID ADJ66570 standard; protein; 760 AA.
XX
AC ADJ66570;
XX
DT 06-MAY-2004 (first entry)
XX
DE Transferrin receptor for anti-cancer protein complex.
XX
KW neuroprotective; cytostatic; gene therapy; protein complex;
KW cellular network; cancer; neurodegenerative disease; drug target.
XX
OS Homo sapiens.
XX
PN WO2004009622-A2.
XX
PD 29-JAN-2004.
XX
PF 18-JUL-2003; 2003WO-EP007835.
XX
PR 19-JUL-2002; 2002EP-00016109.
PR 19-JUL-2002; 2002EP-00016111.
PR 19-JUL-2002; 2002EP-00016123.
PR 19-JUL-2002; 2002EP-00016128.
PR 22-JUL-2002; 2002EP-00016427.
XX
PA (CELL-) CELLZOME AG.
XX
PI Merino A, Bouwmeester T, Bauer A, Drewes G, Marzioch M, Kruse U;
PI Superti-Furga G, Eberhard D, Ruffner H, Hobson S, Helftenbein G;
PI Cruciat C;
XX
DR WPI; 2004-123372/12.
XX
PT New protein complexes of cellular networks underlying the development of
PT cancer and other diseases, useful for diagnosing and/or treating
PT neurodegenerative diseases or cancer, and in drug screening.
XX
PS Disclosure; SEQ ID NO 100; 809pp; English.
XX
CC The invention relates to a protein complex of cellular networks
CC underlying the development of cancer and other diseases. The complex (I)
CC comprises at least one first and second proteins selected from any of the
CC proteins listed in the specification, or their functionally active
CC derivatives, fragments, homologues or variants, the variants being
CC encoded by a nucleic acid that hybridizes to the nucleic acid encoding
CC the protein under low stringency conditions. A complex (II) comprises at
CC least two of the second proteins, where the low stringency conditions
CC comprise hybridization in a buffer comprising 35% formamide, 5 x SSC, 50
CC mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 microg/ml
CC denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20
CC hours at 40 deg C, washing in a buffer consisting of 2 x SSC, 25 mM Tris-
CC HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 deg C, and
CC washing in a buffer consisting of 2 x SSC, 25 mM Tris-HCl (pH 7.4), 5 mM
CC EDTA, and 0.1% SDS for 1.5 hours at 60 deg C. The composition and methods
CC are useful in diagnosing or treating diseases and disorders, preferably
CC neurodegenerative diseases. These may also be used as a drug target or in
CC manufacturing a medicament for the treatment or prevention of the above-
CC mentioned diseases or disorders. The composition may also be used for
CC treating cancer. This sequence represents one of the proteins of the
CC complex of the invention.
XX
SQ Sequence 760 AA;

  Query Match 100.0%; Score 3964; DB 8; Length 760;
  Best Local Similarity 100.0%; Pred. No. 0;
  Matches 760; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLAVDEEENADNNTKANVTKPK 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLAVDEEENADNNTKANVTKPK 60

Qy         61 RCSGSICYGTIAVIVFFLIGFMIGYLGYCKGVEPKTECERLAGTESPVREEPGEDFPAAR 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 RCSGSICYGTIAVIVFFLIGFMIGYLGYCKGVEPKTECERLAGTESPVREEPGEDFPAAR 120
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Qy        121 RLYWDDLKRKLSEKLDSTDFTGTIKLLNENSYVPREAGSQKDENLALYVENQFREFKLSK 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 RLYWDDLKRKLSEKLDSTDFTGTIKLLNENSYVPREAGSQKDENLALYVENQFREFKLSK 180

Qy        181 VWRDQHFVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVTGKLVHANFGTK 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 VWRDQHFVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVTGKLVHANFGTK 240

Qy        241 KDFEDLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVNAELSFFGH 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 KDFEDLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVNAELSFFGH 300

Qy        301 AHLGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAAEKLFGNMEGDCPSDWKTD 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 AHLGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAAEKLFGNMEGDCPSDWKTD 360

Qy        361 STCRMVTSESKNVKLTVSNVLKEIKILNIFGVIKGFVEPDHYVVVGAQRDAWGPGAAKSG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 STCRMVTSESKNVKLTVSNVLKEIKILNIFGVIKGFVEPDHYVVVGAQRDAWGPGAAKSG 420

Qy        421 VGTALLLKLAQMFSDMVLKDGFQPSRSIIFASWSAGDFGSVGATEWLEGYLSSLHLKAFT 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 VGTALLLKLAQMFSDMVLKDGFQPSRSIIFASWSAGDFGSVGATEWLEGYLSSLHLKAFT 480

Qy        481 YINLDKAVLGTSNFKVSASPLLYTLIEKTMQNVKHPVTGQFLYQDSNWASKVEKLTLDNA 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 YINLDKAVLGTSNFKVSASPLLYTLIEKTMQNVKHPVTGQFLYQDSNWASKVEKLTLDNA 540

Qy        541 AFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELIERIPELNKVARAAAEVAGQFVIK 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 AFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELIERIPELNKVARAAAEVAGQFVIK 600

Qy        601 LTHDVELNLDYERYNSQLLSFVRDLNQYRADIKEMGLSLQWLYSARGDFFRATSRLTTDF 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 LTHDVELNLDYERYNSQLLSFVRDLNQYRADIKEMGLSLQWLYSARGDFFRATSRLTTDF 660

Qy        661 GNAEKTDRFVMKKLNDRVMRVEYHFLSPYVSPKESPFRHVFWGSGSHTLPALLENLKLRK 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 GNAEKTDRFVMKKLNDRVMRVEYHFLSPYVSPKESPFRHVFWGSGSHTLPALLENLKLRK 720

Qy        721 QNNGAFNETLFRNQLALATWTIQGAANALSGDVWDIDNEF 760
              |||||||||||||||||||||||||||||||||||||||||
Db        721 QNNGAFNETLFRNQLALATWTIQGAANALSGDVWDIDNEF 760
<!--EndFragment-->
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